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Title: CANINE AND FELINE IMMUNOREGULATORY PROTEINS, NUCLEIC ACID MOLECULES,  
AND USES THEREOF  
Inventor: YANG, SHUMIN

- SEQ ID NO: 4, 6, 7, 8, 9, 11, 18 and 19
- + Oligo search for SEQ ID NO: 4, 6, 7, 8, 9, 11, 18 and 19
- SEQ ID NO: 5 and 10 (PRT).

Prioriy Date: 5/29/1998

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*S. Kaushal*

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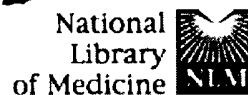
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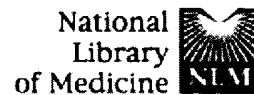
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1: J Interferon Cytokine Res 2000 Sep;20(9):779-85

Related Articles, Links

## Canine interleukin-13: molecular cloning of full-length cDNA and expression of biologically active recombinant protein.

Yang S, Boroughs KL, McDermott MJ.

Heska Corporation, Fort Collins, CO 80525, USA. shumin.yang@maxygen.com

Interleukin-13 (IL-13) regulates immune responses mediated by type 2 T helper lymphocytes (Th2) in the human and mouse. To study the function of this cytokine in the dog, we have isolated a cDNA that encodes the full-length canine IL-13 (CaIL-13) precursor polypeptide of 131 amino acids. CaIL-13 shares significant homology with the IL-13 amino acid sequences of cattle (54.1%), mouse (39.6%), and rat (36.6%) but shares the highest identity with human IL-13 (HuIL-13) (61.8%). The predicted CaIL-13 mature polypeptide of 111 residues was expressed in bacteria, and recombinant CaIL-13 (rCaIL-13) was isolated from inclusion bodies and refolded. rCaIL-13 stimulated the proliferation of TF-1 cells, which are derived from human erythroleukemia cells and respond to IL-13 as well as to a number of other human and murine cytokines. CaIL-13 mRNA was readily detectable by reverse transcriptase-polymerase chain reaction (RT-PCR) in cells from lymph nodes and peripheral blood. The gene sequence and biologically active recombinant protein for CaIL-13 will be useful reagents to determine the role of IL-13 in the regulation of canine immune responses.

PMID: 11032397 [PubMed - indexed for MEDLINE]

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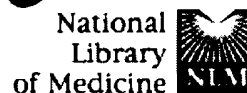
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1: Growth Factors 1993;8(2):87-97

Related Articles Links

## A model for the interaction of the GM-CSF, IL-3 and IL-5 receptors with their ligands.

Goodall GJ, Bagley CJ, Vadas MA, Lopez AF.

Hanson Centre for Cancer Research, Division of Human Immunology, Institute of Medical and Veterinary Science, Adelaide, South Australia.

The high affinity receptors for GM-CSF, IL-3 and IL-5 are heterodimers consisting of a ligand-specific alpha chain and a common beta chain. These proteins are members of a family of proteins known as the "cytokine receptor family" which is characterized by the presence of a 200-residue ligand-binding module. The GM-CSF, IL-3 and IL-5 receptor alpha chains constitute a distinct subgroup and share features not found in other members of the cytokine receptor family, features which we propose to be important for their interaction with the common beta chain and for their binding of the structurally-related ligands. The growth hormone receptor is a well-characterized member of the cytokine receptor family. Based on the structure of the complex between growth hormone and its receptor, we have proposed sites of contact between the GM-CSF, IL-3 and IL-5 receptors and their cognate ligands.

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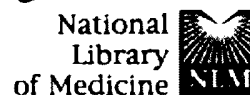
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☐ 1: Exp Hematol 2000 Mar;28(3):231-43

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**FULL-TEXT ARTICLE**

## **A model for assembly and activation of the GM-CSF, IL-3 and IL-5 receptors: insights from activated mutants of the common beta subunit.**

**D'Andrea RJ, Gonda TJ.**

Hanson Centre for Cancer Research and, Adelaide, South Australia, Australia.

Granulocyte-macrophage colony stimulating factor (GM-CSF), Interleukin-3 (IL-3) and Interleukin-5 (IL-5) have overlapping, pleiotropic effects on hematopoietic cells, including neutrophils, eosinophils, monocytes and early progenitor cells. The high-affinity receptors for human GM-CSF, IL-3, and IL-5 share a common beta-subunit (hbeta(c)), which is essential for signalling and plays a major role in recruiting intracellular signalling molecules. While activation of the cytoplasmic tyrosine kinase JAK2 appears to be the initiating event for signalling, the immediate events that trigger this are still unclear. We have isolated a number of activated mutants of hbeta(c), which can be grouped into classes defined by their state of receptor phosphorylation, their requirement for alpha subunit as a cofactor, and their activities in primary cells and cell lines. We discuss these findings with regard to the stoichiometry, activation, and signalling of the normal GM-CSF/IL-3/IL-5 receptor complexes. Specifically, this work has implications for the role of the ligand-specific alpha-subunits in initiating the signalling through the beta-subunit, the role of beta subunit dimerization as a receptor trigger, and the function of receptor tyrosine phosphorylation in generating growth and survival signals. Based on the properties of the activated mutants and the recent structures of erythropoietin receptor (Epo-R) complexes, we propose a model in which (1) activation of hbeta(c) can occur via alternative states that differ with respect to stoichiometry and subunit assembly, but which all mediate proliferative responses, and (2) each of the different classes of activated mutants mimics one of these alternative states.

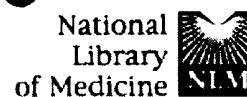
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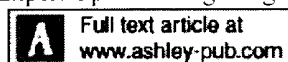
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1: Expert Opin Investig Drugs 2000 Mar;9(3):491-6

Related Articles, Links



## IL-5: biology and potential therapeutic applications.

Weltman JK, Karim AS.

Department of Medicine, Brown University School of Medicine, Providence, RI 02912, USA.  
joel.weltman@brown.edu

IL-5 is the predominant cytokine associated with antigen-induced eosinophilic inflammation in the lung. The activation of Th-2 cells leads to the production of IL-5. The pro-eosinophilic effects of IL-5 include: (1) enhanced replication and differentiation of eosinophilic myelocytes; (2) enhanced degranulation of eosinophils; (3) prolonged survival time of eosinophils; and (4) enhanced adhesion of eosinophils. The effects of IL-5 are mediated via the interaction of IL-5 with receptors (IL-5R) that are expressed on the eosinophil cell membrane. Intracellular signalling produced by occupation of the IL-5R by IL-5 occurs via the JAK-STAT system. IL-5 is a 45 kDa glycoprotein consisting of two identical polypeptide chains. The 5'-promoter region of the IL-5 gene contains elements that are down-regulated by glucocorticoids. Anti-IL-5 reagents have the potential to suppress IL-5 activity without the side effects of glucocorticoids. Studies using monoclonal antibodies (mAbs) against IL-5 have established the feasibility of suppressing eosinophilic inflammation by specifically blocking IL-5 activity. Studies with antisense IL-5 are beginning to provide the basis for non-glucocorticoid, sequence-specific oligonucleotide inhibitors of IL-5. Research has begun on the development of mAbs and antisense oligonucleotide inhibitors of IL-5 that can be inhaled and applied topically.

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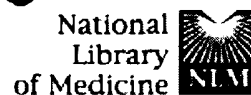
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1: Nippon Rinsho 2001 Oct;59(10):1894-9

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## [Inflammatory cytokines (IL-4, IL-5 and IL-13)]

[Article in Japanese]

Maeda S, Yanagihara Y.

Clinical Research Center, National Sagamihara Hospital.

The polarized Th2 cells play an important role in the pathogenesis of atopic asthma as well as in the induction of airway inflammation. Th2 cytokines, such as IL-4, IL-5 and IL-13, are pivotal in regulating the allergic phenotype, the IgE response or the inflammatory cell-mediated function. Selective inhibition of Th2 cytokines by pharmacologic agents, including anti-cytokine blocking antibody, cytokine mutant and soluble cytokine receptor, will contribute to asthma therapy. Strategies based on blocking key signaling cytokines are also discussed.

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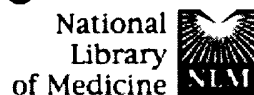
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☐ 1: Pharmacol Ther 2002 Jun;94(3):253-64

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**FULL-TEXT ARTICLE**

## Interleukins-4, -5, and -13: emerging therapeutic targets in allergic disease.

Foster PS, Martinez-Moczygemba M, Huston DP, Corry DB.

Division of Biochemistry and Molecular Biology, John Curtin School of Medical Research, Australian National University, Canberra, ACT 0200 Australia.

For the first time, allergic diseases have emerged as major public health concerns. Highly effective therapies for allergic disease now exist, but are plagued by serious side effects and the fact that a significant minority of patients remains unresponsive. Studies from many laboratories have established that T helper type 2 (T(H)2) cytokines contribute importantly to diseases such as asthma, and therapeutic strategies that target the key T(H)2 cytokines are of potential benefit in allergic disease. In this article, we will review the biology of the T(H)2 cytokines interleukin (IL)-4, IL-5, and IL-13 and their receptors, and will consider several novel strategies to neutralize these molecules in human and experimental asthma. While promising, newer therapies face a gauntlet of developmental challenges, but offer the hope of reducing allergic diseases once again to minor public health concerns. Copyright 2002 Elsevier Science Inc.

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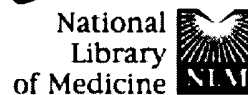
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1: J Interferon Cytokine Res 2001 Jun;21(6):361-7

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## Canine interleukin-5: molecular characterization of the gene and expression of biologically active recombinant protein.

Yang S, Sellins KS, Weber E, McCall C.

Heska Corporation, Fort Collins, CO 80525, USA.

Interleukin-5 (IL-5), which is produced primarily by type 2 T helper lymphocytes (Th2), is an eosinophil differentiation and activation factor. Increased numbers of eosinophils in peripheral blood or tissues (eosinophilia) are observed in asthmatic human patients, in animals with helminth infections, and in dogs with allergic diseases. Antagonism of IL-5 activity is being explored as a potential treatment of a number of disease conditions associated with eosinophils in animal models. In order to study the expression and function of this cytokine in the dog, we have isolated and characterized the canine IL-5 gene. The canine IL-5 polypeptide deduced from the cDNA is composed of 134 amino acids that share varying degrees of homology with IL-5 isolated from several mammals. The genomic structure of the canine IL-5 gene consists of four exons and three introns in the coding region, similar to that of the previously characterized human and mouse IL-5 genes. Recombinant canine IL-5 protein, expressed in *Pichia pastoris*, is biologically active in a cell proliferation assay. Canine IL-5 gene sequences and the biologically active protein described in this study will be useful reagents for future studies of this cytokine in physiologic processes and in pathologic conditions of the dog.

PMID: 11440633 [PubMed - indexed for MEDLINE]

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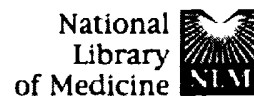
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1: EMBO J 1994 Nov 1;13(21):5176-85

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**Three residues in the common beta chain of the human GM-CSF, IL-3 and IL-5 receptors are essential for GM-CSF and IL-5 but not IL-3 high affinity binding and interact with Glu21 of GM-CSF.**

**Woodcock JM, Zacharakis B, Plaetinck G, Bagley CJ, Qiyu S, Hercus TR, Tavernier J, Lopez AF.**

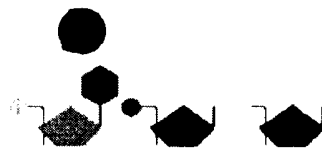
Division of Human Immunology, Hanson Centre for Cancer Research, Institute of Medical and Veterinary Science, Adelaide, South Australia.

The beta subunit (beta c) of the receptors for human granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-3 (IL-3) and interleukin-5 (IL-5) is essential for high affinity ligand-binding and signal transduction. An important feature of this subunit is its common nature, being able to interact with GM-CSF, IL-3 and IL-5. Analogous common subunits have also been identified in other receptor systems including gp130 and the IL-2 receptor gamma subunit. It is not clear how common receptor subunits bind multiple ligands. We have used site-directed mutagenesis and binding assays with radiolabelled GM-CSF, IL-3 and IL-5 to identify residues in the beta c subunit involved in affinity conversion for each ligand. Alanine substitutions in the region Tyr365-Ile368 in beta c showed that Tyr365, His367 and Ile368 were required for GM-CSF and IL-5 high affinity binding, whereas Glu366 was unimportant. In contrast, alanine substitutions of these residues only marginally reduced the conversion of IL-3 binding to high affinity by beta c. To identify likely contact points in GM-CSF involved in binding to the 365-368 beta c region we used the GM-CSF mutant eco E21R which is unable to interact with wild-type beta c whilst retaining full GM-CSF receptor alpha chain binding. Eco E21R exhibited greater binding affinity to receptor alpha beta complexes composed of mutant beta chains Y365A, H367A and I368A than to those composed of wild-type beta c or mutant E366A. These results (i) identify the residues Tyr365, His367 and Ile368 as critical for affinity conversion by beta c, (ii) show that high affinity binding of GM-CSF and IL-5 can be dissociated from IL-3 and (iii) suggest that Tyr365, His367 and Ile368 in beta c interact with Glu21 of GM-CSF.

PMID: 7957082 [PubMed - indexed for MEDLINE]

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☐ 1: AF331920. Canis familiaris ...[gi:15919182]

Links

LOCUS AF331920 1658 bp DNA linear MAM 04-OCT-2001

DEFINITION Canis familiaris interleukin-5 gene, complete cds.

ACCESSION AF331920

VERSION AF331920.1 GI:15919182

KEYWORDS .

SOURCE Canis familiaris (dog)

ORGANISM Canis familiaris

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;

Mammalia; Eutheria; Carnivora; Fissipedia; Canidae; Canis.

REFERENCE 1 (bases 1 to 1658)

AUTHORS Yang, S., Sellins, K.S., Weber, E. and McCall, C.

TITLE Canine interleukin-5: molecular characterization of the gene and expression of biologically active recombinant protein

JOURNAL J. Interferon Cytokine Res. 21 (6), 361-367 (2001)

MEDLINE 11334408

PubMed 11440638

REFERENCE 2 (bases 1 to 1658)

AUTHORS Yang, S.

TITLE Direct Submission

JOURNAL Submitted (22-FEC-2000) Immunology, Heska Corporation, 1613

Prospect Parkway, Ft Collins, CO 80525, USA

FEATURES Location/Qualifiers

source

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mRNA

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5'UTR

1..26

CDS

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3'UTR

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121 agaccttgac actgctctcc actcatcgaa cttggctgat aggcgatggg gtaattttct
181 ttttgattcc tacagtcttt aaaatgcacg ggtaattggt ggtggtggct agtttttaaa
241 gatccattat caataatgaa gtaataagtc ttaataatat ataattgggt accatggtac
301 taagaaagat tataattaaa gttatgaacc ttataatata ttaaaatgga atgttggttc
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 1621 agaacaaaac ggcttattgt agtgggaagt ttgggaga

//

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1: AF331919. Canis familiaris ...[gi:15919180]

Links

LOCUS AF331919 610 bp mRNA linear MAM 04-OCT-2001

DEFINITION Canis familiaris interleukin-5 mRNA, complete cds.

ACCESSION AF331919

VERSION AF331919.1 GI:15919180

KEYWORDS

SOURCE Canis familiaris (dog)

ORGANISM Canis familiaris

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;  
Mammalia; Eutheria; Carnivora; Fissipedia; Canidae; Canis.

REFERENCE 1 (bases 1 to 610)

AUTHORS Wang, S., Seiling, K.S., Weber, E. and McCall, C.

TITLE Canine interleukin-5: molecular characterization of the gene and  
expression of biologically active recombinant protein

JOURNAL J. Interferon Cytokine Res. 21 (6), 361-367 (2001)

MEDLINE 11336431

EVIDENCE 144183

REFERENCE 2 (bases 1 to 610)

AUTHORS Yang, S.

TITLE Direct Submission

JOURNAL Submitted (12-DEC-2000) Immunology, Heska Corporation, 1613

Prospect Parkway, Ft Collins, CO 80525, USA

FEATURES

source

Location/Qualifiers

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5'UTR

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CDS

29..43

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44..610

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☐ 1: AF331920. *Canis familiaris* ...[gi:15919182]

Links

LOCUS AF331920 468 bp DNA linear MAM 04-OCT-2001

DEFINITION *Canis familiaris* interleukin-5 gene, complete cds.

ACCESSION AF331920 REGION: join(1..170,374..406,1276..1404,1523..1658)

VERSION AF331920.1 GI:15919182

KEYWORDS

SOURCE *Canis familiaris* (dog)ORGANISM *Canis familiaris*

Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Carnivora; Fissipedia; Canidae; Canis.

REFERENCE 1 (bases 1 to 468)

AUTHORS Yang, S., Mellins, E.S., Weber, E. and McCall, C.

TITLE Canine interleukin-5: molecular characterization of the gene and expression of biologically active recombinant protein

JOURNAL J. Interferon Cytokine Res. 21 (6), 361-367 (2001)

MEDLINE 11364405

PubMed 11460633

REFERENCE 1 (bases 1 to 468)

AUTHORS Yang, S.

TITLE Direct Submission

JOURNAL Submitted (22-DEC-2000) Immunology, Heska Corporation, 1613

Prospect Parkway, Ft Collins, CO 80525, USA

FEATURES Location:Qualifiers

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mRNA

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/product="interleukin-5"

5'UTR

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CDS

17..431

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3'UTR

432..468

BASE COUNT 180 a 180 c 110 g 118 t

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181  ttctactcc tgaataataa aatcaccaac tgtgcattaa agaagtttt cagggtatag
241  acacattgaa gaacaaact gccacgggg aggcctgtga taaactattc caaaacttat
301  cttaataaaa agacacata gacacacaaa aaaaaattt tgcagcaaaa agatggagaa
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revised July 9, 2002

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**RPS-BLAST 2.2.5 [Nov-16-2002]**

**Query=** gnl|CDD|8195|AA11\_1[6.1] aa(81-20\_1) interleukin-5 [Canis familiaris]  
(134 letters)

**Database:** cdd.v1.60  
10,013 PSSMs; 2,494,783 total columns

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PSSMs producing significant alignments:

Score  
(bits)      E  
value

- gnl|CDD|8195      pfam02025, IL5, Interleukin 5      186      7e-49

- gnl|CDD|8195, pfam02025, IL5, Interleukin 5.

CD-Length = 108 residues, 99.1% aligned  
Score = 186 bits (473), Expect = 7e-49

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Sbjct: 2 EMSALVKETLALLSTHRTLLIGNETLRI PVPTHKNNHQLCTEPIFQGGIDTLKNQTAQEGAV 61

Query: 85 DKLPQNLSLINEHIERQKNRQAGERWPPVTFELDYLLQVFLGVINTEWT 131  
Sbjct: 62 ETLPQNTSLIKKYIDRQKKKCGEERRRVKQFLDYLLQVFLGVINTEWT 108





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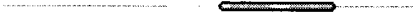
Query: gi|15919183 interleukin-5 [Canis familiaris]  
Matching gi: 15919181

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☐ Plants
☐ Viruses
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134 aa	SCORE	E	ACCESSION	GI	PROTEIN DESCRIPTION
	591	23	AAC54506	3288519	interleukin-5 [Felis catus]
	586	23	AAC27616	3342342	interleukin 5 [Felis catus]
	573	31	AB18348	4461317	Interleukin 5 [Sus scrofa]
	571	26	AAD56791	5690734	interleukin-5; IL-5 [Canis familiaris]
	567	21	AAB11342	1243344	interleukin-5 [Equus caballus]
	551	21	CAAF1704	1113141	interleukin-5 [Bos taurus]
	536	31	AAE10722	890372	interleukin-5 [Ovis aries]
	468	3	AAC05717	2961151	interleukin-5 [Felis catus]
	448	21	AAK18045	15217000	interleukin-5 [Saimiri sciureus]
	430	21	CAA15141	103333	B cell differentiation factor I [Homo sapi
	429	31	AAA19111	514340	interleukin 5
	426	21	AAA16710	644414	interleukin-5
	424	21	CAA15141	254340	B cell differentiation factor I [Homo sapi
	413	31	AAE11700	214413	interleukin-5 [Cavia porcellus]
	386	31	AAG16721	1033467	interleukin-5 [Sigmodon hispidus]
	386	21	AAK15875	729073	interleukin 5
	374	21	CAA19609	12446	IL-5 [Mus musculus]
	370	30	AAD11462	500436	interleukin-5 [Macropus eugenii]
	359	31	CAA11283	314445	interleukin 5 [Rattus rattus]
	352	31	CAA11587	415156	interleukin-5 [Rattus norvegicus]
	349	21	CHULA	1311008	Chain A, Mol_id: 1; Molecule: Interleukin-
	108	20	AAD37461	5006324	interleukin-5 [Sminthopsis macroura]